

## Original Article

# Meta-analysis of the efficacy of 5-aminolevulinic acid photodynamic therapy for the treatment of flat warts

## 統合分析 5-氨基乙酰丙酸光動力療法治療扁平疣的療效

Y Ding, X Li, R Wei, H Fang

**Objective:** We systematically evaluated the efficacy and safety of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) for treating flat warts. **Methods:** Studies in the Wanfang Database, VIP journals, CNKI, PubMed, and EBSCO databases published between January 1990 and September 2015 were retrieved according to the inclusion and exclusion criteria. The studies were screened and evaluated for quality; Review Manager 5.2 software was used to perform meta-analysis of the included studies. **Results:** A total of nine randomised controlled trials comprising 823 patients were enrolled. The meta-analysis results showed that ALA-PDT exhibited better efficacy than CO<sub>2</sub> laser and liquid nitrogen cryotherapy in reducing the relapse rate and adverse reactions and demonstrated a better cure rate than imiquimod cream. **Conclusion:** As ALA-PDT has a low relapse rate and clinical adverse reactions and is effective for the treatment of flat warts.

目的：我們有系統地評估了 5-氨基乙酰丙酸光動力療法治療扁平疣的療效和安全性。方法：根據納入和排除標準檢索 1990 年 1 月至 2015 年 9 月期間發表的萬方數據庫、維普網期刊、中國國知網、PubMed 和 EBSCO 數據庫。對這些研究進行篩選並評估其質量；並用 Review Manager 5.2 軟件對納入的研究進行統合分析。結果：共納入九個隨機對照試驗，當中包括 823 名患者。統合分析結果顯示，5-氨基乙酰丙酸光動力療法在降低復發率和不良反應方面表現出比二氧化碳激光和液氮冷凍療法的療效更好，並且比咪喹莫特乳膏有著更好的治愈率。結論：5-氨基乙酰丙酸光動力療法的復發率 and 臨床不良反應較低，對治療扁平疣實為有效。

**Keywords:** 5-aminolevulinic acid photodynamic therapy, Flat warts, Meta-analysis

關鍵詞：5-氨基酮戊酸光動力治療、扁平疣、Meta 分析

### Department of Dermatology, The First Affiliated Hospital, Zhejiang University, Hangzhou, China

Y Ding, MD, PhD

X Li, MM, MPhil

R Wei, MD, PhD

H Fang, MB, MPhil

Correspondence to: Dr. Y Ding  
Department of Dermatology, The First Affiliated Hospital,  
Zhejiang University, Hangzhou 310003, China

## Introduction

Flat warts are caused by the human papillomavirus (HPV), occurring with a higher frequency in adolescents. They typically manifest as flat papules with normal skin colour or light brown colour and a smooth surface mainly affecting the face, forearms, and back of the hands. Traditional

treatments include salicylic acid, imiquimod, V<sub>A</sub> acids, cryotherapy, autoimmune therapy, or laser therapy, but no single treatment has been shown to completely remove the warts.<sup>1</sup> Moreover, conventional treatment methods cause adverse reactions, such as pain, erythema, hyperpigmentation, or scarring, and show a high recurrence rate resulting in an increased physical and mental burden on patients.

5-aminolevulinic acid photodynamic therapy (ALA-PDT) is a recently developed treatment for flat warts. Advantages of this method include good tolerance, high wart clearance rate, ease of application, repeatable treatment, and can be used in cases with reduced immunity.<sup>2</sup> ALA-PDT has mainly been used to treat superficial skin precancerous lesions and malignant cancers and also for treating viral diseases.<sup>3-5</sup> ALA is the precursor of the endogenous strong photosensitiser protoporphyrin IX (Pp IX); it can penetrate the abnormal stratum corneum and reach the epidermis, wherein ALA is converted to a sufficient amount of Pp IX. When irradiated with visible light, Pp IX releases cytotoxic substances which target the wart cells to induce apoptosis, leaving the surrounding normal tissue cells unaffected.<sup>6,7</sup> In addition to directly eradicating HPV infection, ALA-PDT exhibits immunomodulatory effects on skin lesions.<sup>8-10</sup> ALA-PDT can directly damage the peri-lesional vasculature, interrupting the blood and nutrient supply required for the rapid growth of flat warts.

There has been no systematic analysis of the efficacy and safety of ALA-PDT in treating flat warts and there are no reliable data from large-sample studies supporting the routine application of this new therapy. In this study, we collected and collated the clinical data related to the use of ALA-PDT for treating flat warts. We systematically analysed the efficacy and adverse reactions of ALA-PDT in treating flat warts to evaluate whether this method can be used as a first-line treatment.

## **Materials and methods**

### **Study design**

All studies were randomised controlled trials using ALA-PDT to treat flat warts and were published in Chinese and English.

### **Subjects**

All study subjects had a clinical or histopathological diagnosis of flat warts. Exclusion criteria included those who were allergic to any component of ALA-PDT, cases taking immunosuppressants and corticosteroids, cases suffering from serious medical diseases, or those who were pregnant or lactating patients. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital, Zhejiang University.

### **Interventions**

Flat warts in the experimental group were treated with ALA-PDT, while the control group used traditional therapies such as CO<sub>2</sub> laser treatment, liquid nitrogen cryotherapy, or topical imiquimod cream. Other therapeutic modalities selected as controls included microwave therapy, acupuncture and intramuscular injection of polysaccharide nucleic acid fraction of bacillus Calmette Guérin (BCG-PSN) combined with topical interferon (IFN) gel.

### **Outcome indices**

The cure rate, recurrence rate, adverse reactions, wart clearance rate, and healing quality were evaluated as outcome indices.

### **Data search**

The data were retrieved from the Wanfang Database, VIP journals, CNKI, Pubmed database, and EBSCO database. Studies published between January 1990 and September 2015 were evaluated. Chinese retrieval keywords were flat warts, human papilloma virus, and 5-aminolevulinic acid photodynamic. English retrieval keywords were flat warts, plane warts,

verruca plana, photodynamic therapy, 5-aminolaevulinic acid, and ALA-PDT.

### **Literature screening, extraction, and quality assessment**

The studies were screened, extracted, and cross-checked independently by two reviewers. Disagreement was resolved by discussion or with the aid of a third party.

The following data were extracted from the studies: (a) General information, including title, author, source of journal, and publication time; (b) Research features, including sample size, main ALA-PDT parameters, interventions, and follow-up time; (c) Outcome indices: the relevant outcome indices were summarised.

Study quality was evaluated based on the criteria recommended in the Cochrane handbook version 5.1.0, with the main evaluation items: (a) whether the random method was correct; (b) whether the distribution protocol was concealed; (c) whether a blinded method was used (treatment protocol implementers, study subjects, and evaluators); (d) whether the data were complete; (e) Whether there was selective reporting-caused bias; (f) whether there were other sources of bias. The above quality evaluation criteria were evaluated as "Yes" (low bias), "No" (high bias), or "unclear".

### **Statistical analysis**

Review Manager 5.2 software was used to perform the meta-analysis of the included data. The data were evaluated using the odds ratio (OR) as the effect scale and the 95% confidence interval (95% CI) was determined for each effect indicator. The data were first subjected to the heterogeneity test, followed by fixed-effect model analysis if no heterogeneity was observed among the results ( $P > 0.10$ ,  $I^2 < 50\%$ ). If heterogeneity was present ( $P \leq 0.10$ ,  $I^2 \geq 50\%$ ), the reasons for the heterogeneity were analysed by subgroup analysis. If no cause of heterogeneity was identified, the random-effect model was used for analysis. If the data provided in the studies could

not be combined for analysis, only a descriptive analysis was performed.

## **Results**

### **Literature search**

Ninety-eight relevant studies were preliminarily screened and collected, among which 25 were in English and 73 were in Chinese. After removing 24 studies with repetition of data as well as 68 studies that were irrelevant or did not match the study types based on the title, abstract, and text, nine Chinese studies were included. These studies evaluated a total of 823 patients (treatment group/control group = 405/418).

### **Basic features and quality assessment of the included studies**

The basic features of the included studies are shown in Table 1, while quality assessment is shown in Table 2. These nine randomised controlled trials all utilised randomised grouping, but no specific random method was described. No studies described whether distribution concealment and blinded methods were used. The data in all nine studies were complete, but the presence of bias due to selective reporting and other causes could not be determined.

### **Comparison of ALA-PDT and CO<sub>2</sub> laser treatment**

Three studies<sup>11-13</sup> reported the wart clearance rates of ALA-PDT and CO<sub>2</sub> laser treatment and showed statistical heterogeneity ( $P = 0.0009$ ,  $I^2 = 86\%$ ). Therefore, the random-effect model was used for analysis. The results showed that the two groups were not significantly different [OR=0.35, 95% CI (0.07-1.69),  $P = 0.19$ ] (Figure 1).

### **Recurrence rates of ALA-PDT**

Two studies<sup>11,12</sup> reported the recurrence rates following ALA-PDT and CO<sub>2</sub> laser treatment and showed statistical heterogeneity ( $P = 0.05$ ,

**Table 1.** Basic features of the included literatures

Literature	Cases (T/C)	Main ALA-PDT parameters				Intervention		Follow-up (months)	Observation indexes
		Energy density (J/cm <sup>2</sup> )	Light spot diameter (cm) or wavelength (nm)	Irradiation time (min) (cm)	Frequency	T	C		
Wenwen Zhong 2013	87/90	70 mW/cm <sup>2</sup>	635±5 nm	20	Once/7-10 days, four times at the most	I	III	3	abcd
Xiaomin Chen 2013	30/30	126 mJ/cm <sup>2</sup>	633 nm	–	Once/week, three times at the most	I	III	3	bcde
Jiehua Chen 2015	48/48	60-100 mW/m <sup>2</sup>	633±10 nm	20	Once/10 days, four times at the most	I	III	1	abcde
Yunjie Zhang 2013	52/60	70 mW/cm <sup>2</sup>	635±5 nm	20	Once/10-15 days, four times at the most	I	II	3	abc
Ming Wang 2014	35/35	126 J/cm <sup>2</sup>	633±5 nm	20	Once/week, three times at the most	I	IV	3	abc
Faxing Jiang 2013	16/16	126 J/cm <sup>2</sup>	633±6 nm	20	Once/week, a total of three times	I	IV	6	abc
Haipeng Cao 2015	48/50	80 mW/cm <sup>2</sup>	633±10 nm	20	Once/week, a total of three times	I	V	6	abc
Junqing Ding 2015	44/43	120 mW/cm <sup>2</sup>	635 nm	20	Once/10 days, a total of two times	I+VI	VI	2	abc
Yuan Zheng 2015	45/46	90-100 mW/cm <sup>2</sup>	633 nm	20-25	Once/10-15 days, four times at the most	I	VII	3	abc

Note: T: experimental group; C: control group; I: ALA-PDT; II: liquid nitrogen cryotherapy; III: CO<sub>2</sub> laser therapy; IV: topical Imiquimod Cream; V: microwave; VI: acupuncture; VII: IFN gel+BCG-PSN; a. cure rate; b. recurrence rate; c. adverse reactions; d. wart clearance rate; e. healing quality.

**Table 2.** Quality assessment of the included literatures

Literature	Randomised method	Distribution concealment	Blinded method for the researcher	Blinded method for the patients	Blinded method for the evaluators	Integrity of the data	Selective reporting- caused bias	Other bias
Wenwen Zhong	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Xiaomin Chen	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Jiahua Chen	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Yunjie Zhang	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Ming Wang	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Faxing Jiang	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Haipeng Cao	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Junqing Ding	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear
Yuan Zheng	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear

$I^2 = 73\%$ ). Therefore, the random-effect model was used for analysis. The results revealed significant differences between the two groups [OR=0.22, 95% CI (0.05-1.01),  $P=0.05$ ]. Compared with CO<sub>2</sub> laser treatment, ALA-PDT was associated with a reduced recurrence rate three months after treatment (Figure 2).

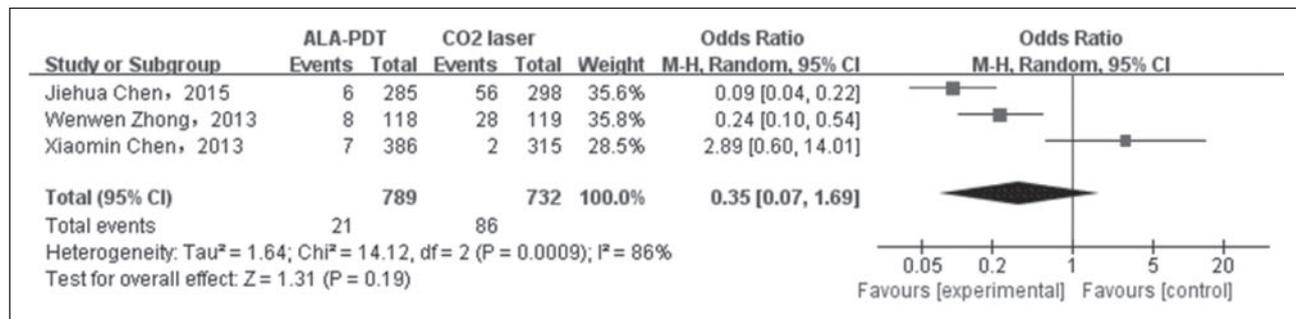
effect model was used for analysis and the results revealed a significant difference between the two groups [OR=0.37, 95% CI (0.26-0.53),  $P<0.00001$ ]. Compared with CO<sub>2</sub> laser treatment, ALA-PDT showed reduced number of adverse reactions (Figure 3).

## Adverse reactions of ALA-PDT

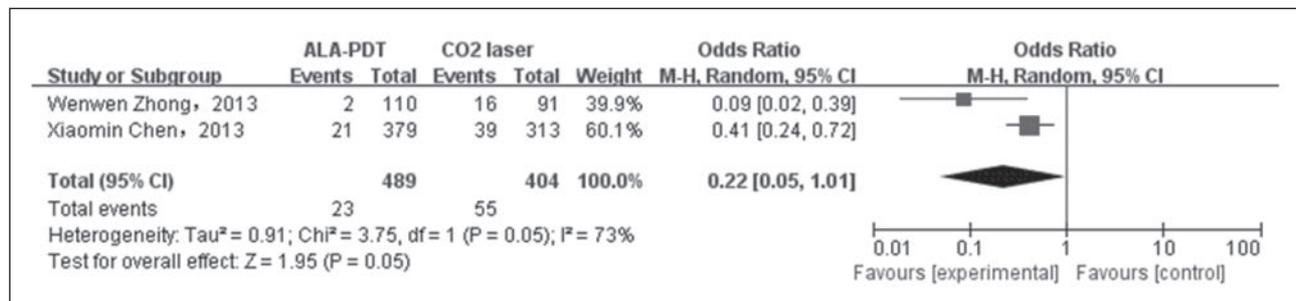
Three studies<sup>11-13</sup> reported the adverse reactions of ALA-PDT and CO<sub>2</sub> laser treatment, such as pain and erythema, and showed statistical heterogeneity ( $P=0.08$ ,  $I^2=59\%$ ). The random-

## Therapeutic efficacy

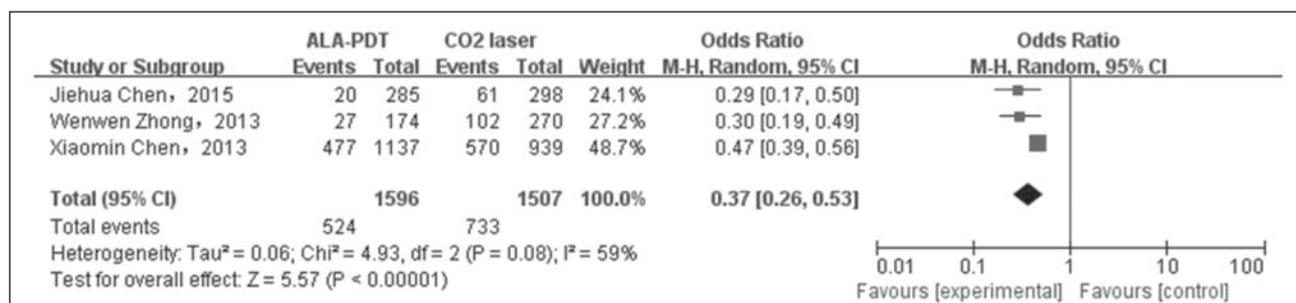
Two studies<sup>12,13</sup> reported the healing effects of ALA-PDT and CO<sub>2</sub> laser treatment. The Vancouver scarring scale was used to evaluate the four indices (colour, thickness, softness, and vascular distribution). The studies exhibited statistical



**Figure 1.** Meta-analysis of ALA-PDT and CO<sub>2</sub> laser in wart clearance rate.



**Figure 2.** Meta-analysis of ALA-PDT and CO<sub>2</sub> laser in recurrence rate three months later.



**Figure 3.** Meta-analysis of ALA-PDT and CO<sub>2</sub> laser in adverse reactions.

heterogeneity ( $P < 0.00001$ ,  $I^2 = 98\%$ ); thus, the random-effect model was used for analysis. The results revealed a significant difference between the two groups [OR=0.06, 95% CI (0.01-0.61),  $P = 0.02$ ]. Compared with CO<sub>2</sub> laser treatment, ALA-PDT exhibited advantages in late healing quality (Figure 4).

### **Comparison of ALA-PDT and topical imiquimod cream for treating flat warts**

Two studies<sup>14,15</sup> reported the cure rates of ALA-PDT and topical imiquimod cream and exhibited statistical heterogeneity ( $P = 0.87$ ,  $I^2 = 0\%$ ), therefore the fixed-effect model was used for analysis. The results showed that the two groups were significantly different [OR=0.02, 95% CI (0.00-0.08),  $P < 0.00001$ ]. Compared with topical imiquimod cream, ALA-PDT was significantly more effective for treating flat warts (Figure 5).

Two studies<sup>14,15</sup> reported on the adverse reactions of ALA-PDT and topical imiquimod cream and showed no statistical heterogeneity ( $P = 0.28$ ,  $I^2 = 13\%$ ). The fixed-effect model analysis revealed that the two groups were significantly different [OR = 2.22 (1.28-3.84),  $P = 0.005$ ]. The incidence of adverse reactions following treatment with topical imiquimod cream was lower than that for ALA-PDT (Figure 6).

### **Comparison of ALA-PDT and liquid nitrogen cryotherapy**

Only one randomised controlled study evaluated the treatment of flat warts by ALA-PDT and liquid nitrogen cryotherapy, consisting of 50 and 56 patients, respectively.<sup>16</sup> While the control group was treated with cryotherapy, the treatment group was given 5-ALA-PDT with the LED irradiation of a power density of 70 mW/cm<sup>2</sup> at a distance of 20 cm, which lasted for 20 minutes each time. The clinical effects, the adverse reactions and the recurrence rate were evaluated 20 days, 3 and 6 months after the last treatment. The results revealed significant differences between the two groups. Compared with the cure rate of 71.4% in the cryotherapy group after one to four treatment

sessions, the cure rate of 92% in the ALA-PDT group indicated that the ALA-PDT was more significantly efficacious than cryotherapy for flat warts ( $P < 0.05$ ). The recurrence rate of 6% in the ALA-PDT group was significantly lower than 21.4% in the cryotherapy group ( $P = 0.03$ ). Compared with 56 cases of mild oedematous erythema and 16 cases of transitory pigmentation in cryotherapy group, the adverse reaction events with 16 cases of mild oedematous erythema and 10 cases of transitory pigmentation in ALA-PDT group were lower than those following cryotherapy ( $P < 0.00001$ , Table 3).

### **Comparison of ALA-PDT and other therapeutic modalities for treating flat warts**

Other therapeutic modalities for treating flat warts had been compared with ALA-PDT through randomised controlled studies, including microwave therapy,<sup>17</sup> acupuncture,<sup>18</sup> and intramuscular injection of BCG-PSN combined with topical IFN gel (Table 4).<sup>19</sup> Compared with other therapeutic modalities, these results indicated that ALA-PDT was superior in terms of cure rate, recurrence rate and adverse reactions.

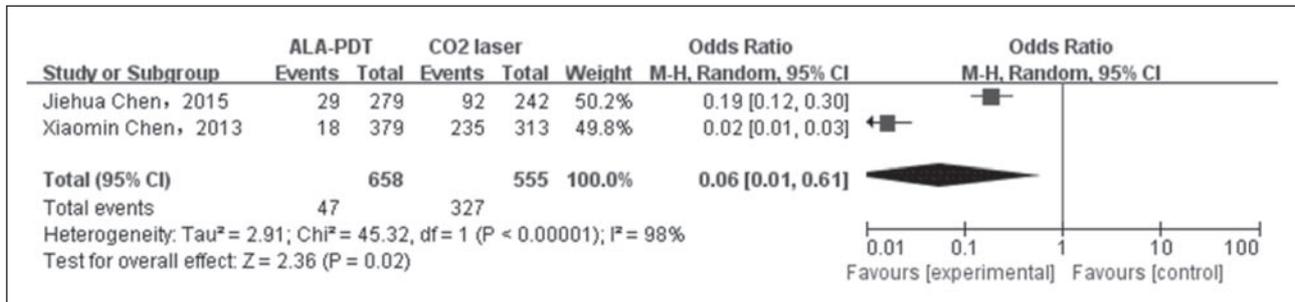
## **Discussion**

In this study, we searched literature databases and evaluated nine studies including 405 cases treated with ALA-PDT and 418 cases treated with conventional treatments (e.g. CO<sub>2</sub> laser, liquid nitrogen cryotherapy, and topical imiquimod cream, etc.). According to the different outcomes of the studies, the advantages and disadvantages of ALA-PDT compared to those of traditional treatment methods were evaluated by meta-analysis. Our results showed that ALA-PDT was superior to CO<sub>2</sub> laser and liquid nitrogen cryotherapy in the treatment of flat warts in terms of recurrence rate and adverse reactions. ALA-PDT had a better cure rate than topical imiquimod, which may be because ALA-PDT not only directly kills wart target cells, but also enhances immune

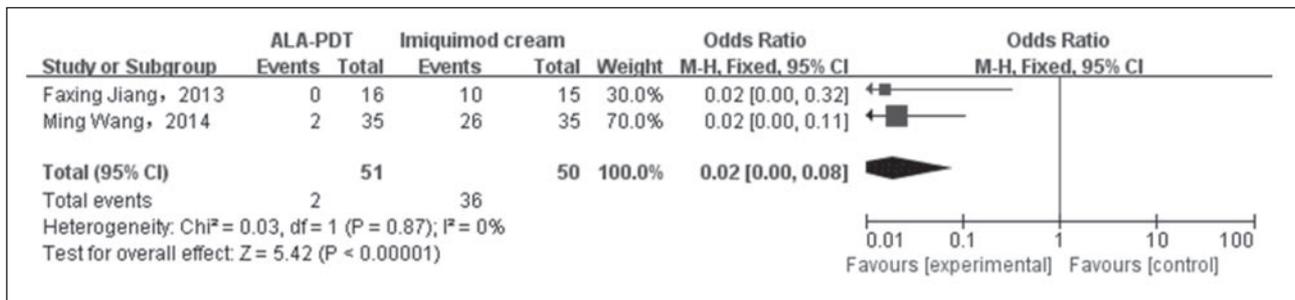
function in the body. Therefore, immunotherapy was effective against HPV infection<sup>20-22</sup> and ALA-PDT showed good efficacy for treating flat warts. Thus, use of this treatment should be increased.<sup>23</sup>

In this study, we evaluated different outcome indices in different control groups. For example, the comparison of the efficacies of ALA-PDT and CO<sub>2</sub> laser was performed using the total wart clearance rate, while the cure rate was used to compare ALA-PDT with topical imiquimod cream. This is because the cure rates and total wart clearance rates calculated based on the number of patients in the selected studies could not be

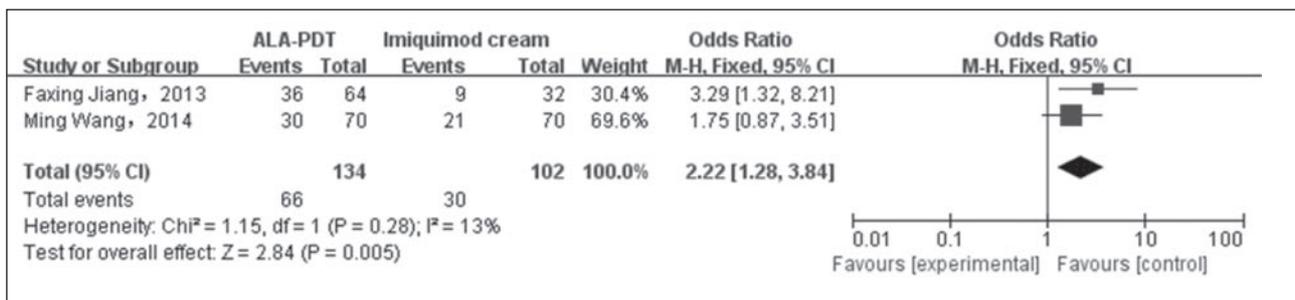
combined for analysis. In addition, the results showed that the incidence rate of adverse reactions following treatment with topical imiquimod cream was lower than that following ALA-PDT, and that following ALA-PDT was lower than with CO<sub>2</sub> laser and cryotherapy. These results demonstrate that the adverse reactions of physical treatments were higher than those of simple topical immunomodulator therapy, which is consistent with clinical experience. These adverse reactions were mainly evaluated based on patients' subjective perceptions (pain) and evaluators' observation of erythema, hyperpigmentation, and scarring as evaluation indices.



**Figure 4.** Meta-analysis of ALA-PDT and CO<sub>2</sub> laser in healing quality.



**Figure 5.** Meta-analysis of ALA-PDT and topical imiquimod cream in cure rate.



**Figure 6.** Meta-analysis of ALA-PDT and topical imiquimod cream in adverse reactions.

Comparisons of ALA-PDT and other therapeutic modalities for treating flat warts are summarised and described in this article. These results supported that ALA-PDT was superior for treating flat warts in terms of cure rate, recurrence rate and adverse reactions. There were some limitations to these studies. All the studies used randomised grouping but did not explain the specific grouping methods. The distribution concealment and blinding methods were not specifically described, and thus the study designs may have exhibited bias. These limitations can be overcome by conducting additional high-quality randomised controlled trials in the future.

In this study, 25 English papers were searched in Pubmed. Six overseas randomised controlled clinical trials about PDT treatment on multiple warts were reported from South Korea, Japan,

Singapore and North Europe. These studies focused on viral warts and genital warts, which are different from the aim of our study and were therefore difficult to be included in this meta-analysis. No overseas randomised controlled clinical trials on ALA-PDT in the treatment of flat warts were found. One Chinese randomised controlled clinical trial was published in English.<sup>24</sup> The efficacy and safety of ALA-PDT with different concentrations of photosensitiser in the treatment of generalised recalcitrant facial verruca plana has been investigated with the conclusion that PDT with ALA of 10% concentration offers better efficacy and safety than 5% or 20% concentration.

In summary, ALA-PDT is a new therapy that shows rapid improvement and is associated with less side effects compared with the conventional CO<sub>2</sub> laser, cryotherapy, topical imiquimod cream and other

**Table 3.** The therapeutic efficiency and safety of photodynamic therapy and cryotherapy on flat wart<sup>16</sup>

Group	Total Cases	Invalid (case/rate)	Effective (case/rate)	Cure (case/rate)	Recurrence (case/rate)	Adverse reactions	
						Edematous erythema (case/rate)	Pigmentation (case/rate)
ALA-PDT	50	0/0%	4 (8%)	46 (92%)*	3 (6.0%)*	16 (32%)*	10 (20%)
Cryotherapy	56	0/0%	16 (28.6%)	40 (71.4%)	12 (42.4%)	56 (100%)	16 (8.6%)

Note: \*represents P<0.05

**Table 4.** The efficiency and safety of photodynamic therapy and other therapeutic modalities on flat wart<sup>17-19</sup>

Clinical Trail	Total Cases	Invalid (case/rate)	Effective (case/rate)	Cure (case/rate)	Recurrence (case/rate)	Adverse reactions			
						Pain (case/rate)	Oedematous erythema (case/rate)	Scar (case/rate)	Pigmentation (case/rate)
1 ALA-PDT <sup>19</sup>	45	0 (0%)	45 (100%)	38 (84.44%*)	0 (0%)	2 (4.44%)	5 (11.11%)	–	13 (28.89%)
IFN gel+ BCG-PSN	46	5 (10.87%)	41 (89.13%)	28 (60.87%)	1 (2.17%)	–	8 (17.39%)	–	13 (28.26%)
2 ALA-PDT <sup>17</sup>	48	0 (0%)	48 (100%*)	44 (91.67%)	0 (0%*)	8 (16.67%*)	12 (25%*)	0 (0%*)	8 (16.67%*)
Microwave	50	5 (10%)	29 (58%)	15 (30%)	25 (50%)	20 (40%)	20 (40%)	4 (8%)	16 (32%)
3 ALA-PDT+ acupuncture <sup>18</sup>	44	2 (4.54%)	29 (65.91%)	86.36%*	3 (10.34%*)	10 (22.73%)			
Acupuncture	43	9 (20.93%)	21 (48.84%)	65.12%	8 (38.1%)	7 (16.28%)			

Note: \*represents P<0.05

therapeutic modalities. ALA-PDT can be used to effectively treat flat warts, reduce the recurrence rate, and reduce the incidence of adverse reactions. Thus, the clinical use of this method should be increased.

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## Conflicts of interest

All of the authors declare that they have no conflicts of interest regarding this paper.

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